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REMARKS

Entry of the Amendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.114, are thus respectfully requested.

1. Status of the Claims

Claims 54-73, 76, and 78-98 are pending. Claims 78, 80, 81 and 84-93 stand withdrawn. Claims 54-73, 76, 79, and 94-98 stand rejected.

Withdrawn Claims. Applicants note that the Office incorrectly lists at least claims 78, 80, 81, and 93 as being withdrawn. The Office alleged in the Office Action mailed July 13, 2006 that these claims were drawn to non-elected subject matter. Applicants disagree. Applicants elected SEQ ID NO: 20 for search purposes. Claim 93 refers to SEQ ID NO: 20. Claims 78, 80, 81, and 93 depend from claim 54 and would encompass the elected species. Applicants have indicated the status in the instant amendment as "Previously Presented" instead of "Withdrawn."

After entry of the amendments, claims 63 and 69 stand canceled. Applicants have amended claims 54 and 72. The amendments to the claims have been made without prejudice to or disclaimer of the subject matter contained therein. Applicants reserve the right to file a continuation or divisional application on any subject matter cancelled by way of this or any amendment. Claims 54 and 72 cancel recitation of duplicative sequence identifiers. Thus, the amendments are supported by at least by the original claims as filed.

2. Acceptance of the Drawings

Applicants note with appreciation the indication that the drawings submitted January 16, 2007, are acceptable.

3. Information Disclosure Statements

Upon review of the file, Applicants noted that the Information Disclosure Statement submitted September 15, 2003, does seem to have been considered. Applicants respectfully request an initialed copy of the PTO-1449 form relating to this IDS reflecting acknowledgement with the Office's next communication.

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4. Election/Restrictions

As noted, SEQ ID NO: 20 was provisionally elected for search purposes only by Applicants on May 19, 2006. No art was identified with regard to SEQ ID NO: 20. The remaining sequences must now be searched. A peptide of interest was also elected for search purposes only, SEQ ID NO: 27. Applicants point out that upon allowance of the generic claims, applicants will be entitled to consideration of the claims to the additional species as discussed in the Office Action dated September 8, 2005, at page 3.

5. Objection to the Specification

The specification is objected to as allegedly introducing new matter, because SEQ ID NO: 22 and 23 are the same and allegedly unsupported by Figures 12 and 13. Applicants submit herewith a substitute Sequence Listing, which remedies the identified errors in SEQ ID NOS: 22 and 23, along with a paper copy and Declaration pursuant to 37 C.F.R. § 1.821-1.825 (*i.e.*, SEQ ID NOS: 22 and 23 have been corrected to have residue 144 as a Gly and for SEQ ID NO: 23, the additional change of reciting a PRO at position 152). With this submission, the objection stands mooted and should be withdrawn. No prohibited matter is believed to have been introduced with this submission.

Applicants note that apparently SEQ ID NOS: 22 and 23 as depicted in Figures 12 and 13 were not searched based on prior art, even though the sequences as depicted in those figures were assessed for patentablility in view of the rejection under 35 U.S.C. § 112, first paragraph. Applicants note that the goal of examination is to attend to these issues early and completely. See M.P.E.P. § 706. Accordingly, search with these corrected sequences is respectfully requested.

Applicants have also amended the paragraph on page 9, line 11-16 (of the substitute clean copy of the specification submitted July 5, 2005 to correctly recite both instances of NaCl. Withdrawal of the rejection is in order.

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6. Objection to the Claims

Claims 63 and 69 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office asserts that the peptides of interest recited in claim 54 are GLP-1 derivatives that inherently have insulinotropic activity, and therefore the claims are not further limiting. Applicants have cancelled the claims thereby mooting the objection. Accordingly, the objection should be withdrawn.

7. Rejections under 35 U.S.C. § 112, First Paragraph (Written Description)

7.1 Claim 97

Claim 97 is rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, because the error in the sequence listing, the Office rejected claim 97 with respect to SEQ ID NOS: 22 and 23. Applicants submit herewith a substitute sequence listing which correctly sets forth the sequences displayed in Figures 12 and 13. Accordingly, the rejection of claim 97 is mooted and should be withdrawn.

Applicants note that SEQ ID NO: 20 stands free of any art.

7.2 Claims 54-73, 76, 79, 94-96 and 98

Claims 54-73, 76, 79, 94-96, and 98 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. The Office acknowledges that with regard to the genus of peptides of interest, the rejection has been withdrawn in view of the Amendment. Office Action, page 5.

The Office has reinstated the rejection of lack of written description with regard to the genus of protective peptides and the genus of helper peptides. *Id.* The Office alleges that the "specification fails to describe any other representative species by any identifying characteristics or properties other than functionality of encoding a protective or helper

peptide and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest." *Id.*

Applicants traverse the rejection. To satisfy the written description requirement, the applicant must convey to the skilled artisan that, as of the filing date sought, the applicant was in possession of the invention. *See Falkner v. Inglis*, 448 F.3d 1357, 1365, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); *see also* MPEP § 2163.04. Accordingly, the Office must have a reasonable basis to challenge the adequacy of the written description. *See* MPEP § 2163.04.

The description needed to satisfy the requirements of 35 U.S.C. § 112 varies with the nature and scope of the invention at issue and with the scientific and technologic knowledge already in existence. *See, e.g., In re Wertheim,* 541 F.2d at 262, 191 U.S.P.Q. at 96 ("The primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure") (emphasis in original); *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.").

This means that the description requirement is more easily met if a recited genus consists of compounds known in the art, e.g., steroids, as opposed to a recited genus of hypothetical compounds. *Compare Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926-27, 69 U.S.P.Q.2d, 1886, 1894-95 (Fed. Cir. 2004) (finding inadequate written description, where the disclosure provided nothing more than a "hoped-for function for ***an as-yet-to-be-discovered*** compound, and a research plan for trying to find it"), *with Capon*, 418 F.3d at 1358, 76 U.S.P.Q.2d at 1085 (reversing the Board and holding that functionally claimed chimeric genes prepared from ***known DNA sequences of known function*** were adequately described without a description of structure, formula, or chemical name for the nucleotide sequences).

Here, Applicants provide the peptides of interest. The Office admits that the peptides of interest have written description. The Office asserts that the specification lacks a sufficient disclosure for the genus of protective peptides or helper peptides. Applicants point out that designing protective peptides for polypeptides were known in the art at the time. For example, U.S. Patent Nos. 4,366,246, 4,704,362, 4,425,437, and 4,431,739, and related Japanese patent publication No. 54-145289 discuss the use of a peptide linked to a peptide of interest. In this case, the protective peptide used was from β-galactosidase. *See also*, U.S. Patent Nos. 5,670,340 and 6,037,145 for additional protective peptides. Protective peptides are used to prevent decomposition of the polypeptide by the endogenous proteases present in the host cells. In instances wherein the peptide-of-interest is short, these types of peptides can be easily decomposed by the endogenous proteases of cells.

Additionally, the use of protective peptide, also referred to in the industry as carrier sequences, was known as early as the late 1970s. They were used to protect the target proteins from proteolysis in *e.g.*, prokaryotic hosts. *See, e.g.,*

- Itakura et al., 1977, "Expression in Escherichia coli of a Chemically Synthesized Gene for the Hormone Somatostatin," Science 198: 1056-1063; [subject matter of the first 4 patents above].
- Goeddel et al., 1979, "Expression in *Escherichia coli* of Chemically Synthesized Genes for Human Insulin," Proc. Nat'l Acad. Sci. USA 76: 106-110;
- Uhlén and Moks, 1990, "*Gene Fusions for Purposes of Expression: An Introduction*" Methods Enzymol. 185: 129-143; and
- LaVallie and McCoy, 1995, "*Gene Fusion Expression Systems in Escherichia coli*", Curr. Opin. Biotechnol. 6: 501-506.

In this application, the protective peptides protect the combination of the peptide of interest and the helper peptide. Specific types of protective peptides are not required for purposes of written description, as there was sufficient description in the art at the time and when combined with the specification, the skilled artisan would have understood how to make and use the protective peptides in combination with the rest of the fusion proteins.

Applicants point out that the skilled artisan readily could determine the pI's of a protein of interest. On page 10, lines 16-33, Applicants provide the guidelines in order to

prepare the helper peptide for use in context with the peptide of interest. The paragraph is reiterated below for convenience:

> The helper peptide of the present invention may be prepared as appropriate depending on the physicochemical properties of the peptide of interest. For example, when the isoelectric point of the peptide of interest is neutral to weak acid and the optimum pH during the production process is also neutral to weak acid and thereby the solubility of the peptide of interest under such pH is too low, then the helper peptide is preferably designed so that the isoelectric point (pI) of the peptide of interest that has a helper peptide added thereto is 8 to 12 and more preferably 9 to 11. The helper peptide of the present invention may be added to either the N-terminal or C-terminal of the peptide of interest. The dimension (length) of a helper peptide is preferably 5 to 50 amino acid residues, and more preferably from 5 to not greater than 30 amino acid residues, but it contains at least one basic amino acid or acidic amino acid.

Applicants also direct the Office's attention to page 14, lines 3 to page 15, line 6, of the specification, Thus, Applicants provide the structure (length in the claim of 5-50 amino acids) of the helper peptide. The required pI of the helper peptide would be determinable from the pI of the peptide of interest. Determination of the sequences for use as the helper peptide for any specific peptide of interest also would be readily determinable based on the pI of the peptide of interest. The fact that the genus of helper peptides is large does not vitiate the ability to determine helper peptides that would have a different but suitable pI. Determination of appropriate sequences would easily determinable by the use of software at the time. Thus, the structure and properties of the peptide of interest coupled with the function of the peptide of interest and guidance of how to select sufficiently describes the helper peptide.

Turning to the genus of protective peptides, the pI of the helper peptide and peptide of interest would govern the pI of the protective peptide selected. Applicants direct the Office's attention to page 18, line 15. Such protective peptides include but are not limited to peptide fragments from β-galactosidase. Applicants also direct the public to the attention of Japanese Patent Publication No. 54-145289 and related U.S. Patent Nos. 4,366,246, 4,704,362, 4,425,437, and 4,431,739. Other protective peptides selectable based on pI relative to the peptide of interest and helper peptide could similarly be selected and were well known at the

time as discussed above. Applicants are not required to provide structures of known sequences. *See Capon v. Eshhar*, 76 U.S.P.Q. 2d 1078, 1083-86 (Fed.Cir. 2005). The function of the protective peptide is to prevent endogenous degradation. A patent application does not have to provide every single variant or even working examples. Actual reduction to practice of all aspects is not required. *Falkner v. Inglis*, 79 U.S.P.Q.2d 1001, 1007-1008 (Fed. Cir. 2007). The background behind using protective peptides to prevent degradation was known in the art at the time. This information, coupled with the assembly of the other parts and their structural and functional criterion would have provided sufficient information for the skilled artisan to select the appropriate protective given what was known in the art at the time and what is taught by the specification.

Accordingly, Applicants assert that there is sufficient written description for the skilled artisan at the time of the invention to have selected the correct helper peptide and protective peptide for each peptide of interest. Applicants respectfully request withdrawal of the rejection.

8. Rejections under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 54-73, 76, 79, 94-96, and 98 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, "while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures 7, 11-13 (SEQ ID NOs: 20-23), does not reasonably provide enablement for a process of making a peptide of interest of SEQ ID NOs: 27-70 or any other GLP-1 derivative recited in the claims using other helper and protective peptides." Office Action, page 6.

Applicants traverse the rejection. Applicants provide the precise sequence for the peptide of interest. From that the skilled artisan would have readily been able to determine the pI of the peptide of interest. Knowing the pI of the peptide of interest and reading the specification regarding the helper peptide as discussed in Section 7 above, the skilled artisan would have been able to make and use a large number of [helper peptide + peptide of interest] combinations with the appropriate pI. The parameters in the specification provide all the information necessary.

That leaves the choice and addition of a protective peptide. Use of protective peptides was well known in the art at the time as discussed *supra*. Applicants provide examples of

protective peptides, as well as the guidelines for selection. As both the Board of Appeals and Interferences and the Federal Circuit pointed out, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed great expenditures of time and effort were ordinary in the field of vaccine preparation." *Falkner v. Inglis,* 79 U.S.P.Q.2d at 1006. Applicants provided sufficient guidance on how to select the building blocks of helper peptides and protective peptides, given the list of peptides of interest. How to make and use each of the peptide of interest likewise is set forth in the specification. Assessment of the final product would have been well within the scope of the skilled artisan. Thus, there is no undue experimentation required in order to make and use claims 54-73, 76, 79, 94-96, and 98. The rejection therefore should be withdrawn and the claims allowed.

9. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 54-73, 76, 79, and 94-98 stand rejected as indefinite.

9.1 Claims 54-77, 79, 94-96 and 98

Claims 54-77, 79, 94-96 and 98 stand rejected as alleged indefinite. The Office asserts that the claims are confusing, because SEQ ID NOS: 27-70 are the sequences of the GLP-1 derivatives that are recited twice. The Office seeks Applicants to amend the claims to place the sequence identifiers after each GLP-1 derivative.

Applicants have amended the claims such that they no longer recite SEQ ID NOS: 27-70. Accordingly, the rejection is mooted and should be withdrawn.

9.2 Claim 97

Claim 97 is rejected as indefinite, because it is allegedly confusing. The Office asserts the confusion stems from SEQ ID NOS: 22 and 23 being different from Figures 12-13. This rejection is mooted by the submission of the substitute sequence listing which recites sequences that correspond to the figures. Accordingly, the rejection for indefiniteness should be withdrawn.

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10. Claim Rejections under 35 U.S.C. § 102(e)

The Examiner has rejected claims 72, 73 and 76 under § 102(e) as anticipated by Suzuki et al. (U.S. Patent No. 5,891,671). The Office notes that the prior rejection of the process claims in view of Suzuki is withdrawn. Suzuki is alleged to "teach an expression vector comprising a DNA encoding a fusion protein comprising the protective peptide, helper peptide and 7-37 GLP-1 and an *E. coli* transformed with said vector.... Said protective peptide is a fragment of *E. coli* β-galactosidase that is used in the instant invention and cleavage site between a linker peptide and a peptide of interest is a Kex2 protease cleavage site as in the instant invention. The bond between protective and linker peptides represents another cleavage site." Office Action, page 9. The Office then concludes that "absent evidence to the contrary the fusion of the helper peptide and the 7-37 GLP-1 fusion has the requisite pI." Office Action, page 10. Suzuki is further alleged to teach other peptides of interest such as GLP-1 (7-36) NH_2.

Suzuki does not teach or suggest the recited peptides of interest let alone the combination of fusion proteins presented herein. The '671 patent at best teaches a fusion protein comprising [protective peptide]-[linker site]-[peptide of interest]. Applicants' claims are directed to a fusion protein generally described as [protective peptide]-[helper peptide]-[peptide of interest]. No linker site is recited in the composition of the pending claims. Additionally, the '671 patent does not teach or suggest the use of a helper peptide, let alone the order provided.

The example of the '671 patent provides for cleavage of the fusion protein by a Kex2 protease. However, there is no cleavage site between the [protective peptide] and the [linker site]. The current claims have a cleavage site between the [protective peptide] and the [helper peptide] and another cleavage site between the [helper peptide] and the [peptide of interest]. *See e.g.,* claim 1.

The helper peptide is present, as would be understood by the skilled artisan, to modify the physicochemical property of the peptide of interest. As following the description, the fusion protein is first cleaved between the [protective peptide] and the [helper peptide + peptide of interest] so as to liberate the [helper peptide + peptide of interest] portion. The [helper peptide + peptide of interest] is then purified and cleaved again to yield only to the peptide of interest. The fusion protein of the cited '671 cannot be used in this fashion nor

does it suggest the composition presently claimed.Accordingly, Applicants submit that the rejection should be withdrawn and the claims allowed.

11. Allowable Subject Matter

Claims 82 and 83 are objected to as being dependent upon are rejected base claim, but would be allowable if rewritten in independent form.

CONCLUSION

In conclusion, this is believed to be in full response to the outstanding restriction requirement. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience. Should any outstanding fees be owed or overpayments credited, the Commissioner is invited to charge or credit Deposit Account No. 50-0573.

Respectfully submitted,
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